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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/015,469 | 01/29/1998 | HOWARD M. KINGSTON | 04945000095 | 5751 |

7590 06/27/2003

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EXAMINER

SODERQUIST, ARLEN

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| ART UNIT | PAPER NUMBER |
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1743

DATE MAILED: 06/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/015,469

Applicant(s)
Kingston

Examiner
Arlen Soderquist

Art Unit
1743



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jun 17, 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-33 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 5-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 17, 2002 has been entered.

2. Claims 1-3 and 5-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the second to last sub-paragraph of the claim the phrase "while correcting for species conversion" is found. There is no antecedent basis for conversion between species in the claim and therefore the phrase lacks antecedent basis. Additionally it is not clear if the incomplete separation means that less than all of the species in the sample are completely separated from the sample or if the separation does not provide a complete separation between the specie being measured and at least one other specie in the sample. For examination purposes the claim will be treated as a method having the following steps: providing one stable isotope, converting that stable isotope into the species to be measured to form an isotopically labeled specie, spiking the sample with the isotopically labeled specie, equilibrating the spiked sample, performing a separation in which two or more of the sample components are not separated from each other, making isotope ratio determinations for the specie and mathematically deconvoluting the result to correct for the partial separation. With respect to claim 6 it is not clear how the claim further defines over claim 1 since claim 1 requires that the isotopic spikes correspond to the specie to be measured. Relative to claim 32 it is also not clear how the claim provides a further limitation to claim 1.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1 - 3, 5 - 33 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kingston (US 5,414,259) in view of Suzuki-

Sawada (newly cited and applied). In the patent Kingston teaches and claims a method of speciated isotope dilution mass spectrometry. The method of determining the concentration of a specie in a sample is summarized in columns 6-7 and includes providing at least one predetermined, enriched isotope in the same speciated form as the species to be measured, spiking the sample containing the species to be measured, equilibrating the spiked species with the species to be measured, separating the different species in the sample and subsequently determining the concentration of the species to be measured by employing isotopic element specie ratios and deconvoluting any conversion of one species into another. In one embodiment, a single speciated isotope spike is employed and, in others, two or more such spikes may be employed. Column 7 lines 20-23 teach that the steps remain nearly the same when more than one species is spiked however the mathematical deconvolution is different depending on the number of spiked species and the interaction between the species. In a preferred embodiment, time resolution chromatography is used to effect separation of these species from the sample and mass spectrometer is employed in determining isotopic elemental ratios. It is also preferred that a method be employed to determine if there was conversion from one species to another. In another embodiment, spiking of the several different isotopically enriched analogs of the same specie are added at various steps in the sampling procedure and the stability and integrity of the specie with respect to these processes is evaluated by mass spectrometric measurements of the various isotopic ratios. Chemical processes, extraction methods, dissolution procedures and storage procedures are evaluated. In another embodiment, speciated isotope dilution is used to determine the effect on species of various sample preparation methods and portions of sample preparation techniques. Extraction and separation procedures employ the technique to provide definitive evidence of accurate specie manipulation and provide for performance based measurement. Column 8 teaches an equation used in the mathematical deconvolution of the results. The equation of line 45 is taught as one used to calculate the species concentration when there is no species crossover. Column 10, beginning at line 5 and column 11 beginning at line 34, discuss the deconvolution of the results in the actual examples given. Using the equations taught will provide an indication of species interaction or crossover by changes in the isotopic

ratio from the natural abundance for the different species. Column 11, lines 48-55, column 12, lines 27-32, column 13 lines 20-36 and column 14, lines 28 are reproduced below with added emphasis and correction.

“One may determine the extent of conversion of each specie to another, and one or both may need to be corrected for conversion in different examples. *The relative concentration and quantity of each isotope converted to the other can be calculated using mathematical relationships established for the specific isotopes, enrichment factors, and resolutions of the analyzing instrument.*”

“The use of more than one speciated isotope provides the ability to calculate the contribution and conversion of one specie to another. This is very different from current methods wherein only the total in the final form can be determined and conversion is undesirable and unmeasurable.”

“Deconvolution of these species in the presence of each other may be determined using isotopic ratios such as, for example, CR(III) and CR(VI) species crossover by a species III to IV and vice versa shift will result in the isotope d(el)ement specie ratios being altered for each specie. Determination of the amount of crossover of one specie to another by using isotopic ratios to calculate the specie interchange becomes possible, employing the present invention.”

“Even where two isotopic spikes are not available, one spike can be used with calculation of crossover by ratio shift in one specie. An alternative is to perform the same speciated spiking experiment repeatedly but transform the isotopic spike into different species for different experiments. *By collecting multiple measurements and doing a mass balance each time the entire speciation behavior mechanism can be evaluated.*”

“I. Other algorithm calculations are possible from the two components of time resolution of individual species and mass isotopic element specie ratio alterations.”

This clearly shows that determining the extent of crossover was contemplated by Kingston including what kinds of mathematical equations would need to be used. Columns 12 - 16 teach various separation methods, samples, and detection methods that can be used within the scope of the invention. Column 9, lines 50-63 discuss the resolution being the time separation of the species cause by the chromatographic separation. Thus in the above quote the meaning of the “resolutions of the analyzing instrument” means that the resolution is an instrument dependent factor that can be corrected for by using mathematical relationships. Since the reference teaches that mathematical relationships can be established for analyzer dependent effects such as resolution, the Kingston reference anticipates the incomplete separation situation of the claims.

The Kingston reference does not show a situation in which overlapping peaks can be separated, however in the Suzuki-Sawada reference an analysis of oligosaccharides by on-line high-performance liquid chromatography and ion-spray mass spectrometry. Oligosaccharides were analyzed by a combination of HPLC and mass spectrometry (MS). First, oligosaccharides labeled with 2-aminopyridine were studied to see if they could be analyzed by MS under the conditions used for separation by HPLC. Pyridylamino (PA)-oligosaccharides could be analyzed under these conditions, although the mass spectra were affected. Then, liquid chromatography-mass spectrometry was used to analyze a PA-oligosaccharide mixture derived from human IgG. The PA-oligosaccharides were separated on a reversed-phase column and mass-analyzed directly. The observed molecular weights were close to or identical to those expected from the structures, which were estimated from the elution position on HPLC. This method is rapid and simple, as the mass spectrometer can give the accurate molecular weight of each PA-oligosaccharide in one chromatography run, even if the HPLC separation is incomplete. Page 206-207 discuss how the molecular weight information can be used to separate the overlap between different molecules in the mixture. This method can be used to extend the so-called two-dimensional mapping of PA-oligosaccharides. The structure can be studied in greater detail by tandem MS. Thus based on the teachings of Suzuki-Sawada one of ordinary skill in the art would have recognized, understood or expected the combination of chromatography with mass spectrometric detection to resolve problems of incomplete separation when the mass of the specie differ.

5. Applicant's arguments filed June 17, 2002 have been fully considered but they are not persuasive. Relative to the arguments concerning correcting for species conversion, applicant is directed to the claim 1 which does not require that species conversion is occurring. Thus these arguments are not commensurate in scope with the claims. Additionally only one isotopically enriched specie is required for the method of claim 1. Relative to the anticipation by the Kingston reference, applicant is directed to the fact that the Kingston reference is directed toward the technique of **speciated** isotope dilution mass spectrometry (see title). As such it does not suffer the problems of isotope dilution mass spectrometry! Furthermore claim 1 does not require the analysis of more than one specie or that there is conversion between species. The claim is

also not clear relative to what constitutes an incomplete separation. Relative to the incomplete separation, the reference teaches that mathematical equations can be used to correct for the resolution of the analysis instrument. Within this scope each and every limitation of the anticipated claims are clearly and totally taught as set forth above. As further evidence of this examiner has provided the Suzuki-Sawada reference teaching that when chromatography and mass spectrometric detection are combined, the different masses of the specie within the sample can be used to separate the different specie even though the chromatography is unable to effect a complete separation. Thus one of the are would recognize that the combination of chromatography and mass spectrometry as taught by Kingston would inherently be capable of separating specie that are not completely separated by chromatography alone. Applicant argued that relative to claim one the Kingston reference does not teach the ability to provide a different isotopic spike for each species with subsequent deconvolution of the species concentration while correcting for conversion. First it is pointed out that this scope includes a single species and a single isotopic spike. Second Applicant is directed to the specific quotes from Kingston listed above as evidence that a single or multiple spike was fully anticipated by Kingston. In this same manner each of the dependent limitations is fully anticipated by the Kingston reference. If applicant is trying to argue that the instant claims were not enabled in applicant's prior patent, then applicant has the burden of showing that at least claims 2-8, which deal with multiple species, were not enabled by the disclosure of the Kingston patent.

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The cited art is directed at the use of isotopic labels and mass balance in mass spectrometric analysis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

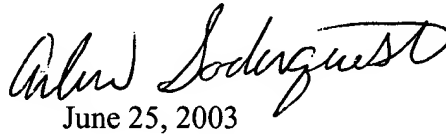
For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Numbers for faxing official papers are 703-872-9310 (before finals), 703-872-9311 (after-final), 703-305-7718, 703-305-5408 and 703-

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305-5433. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.



June 25, 2003

ARLEN SODERQUIST
PRIMARY EXAMINER